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EP 0599589 A1 **EP 0475807 A2**
EP 0371736 A2 **WO 2002/072163 A1**

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(54) Abstract Title: **Wound dressings for the treatment of wound infection**

(57) A wound dressing comprising: a therapeutic agent selected from the group consisting of antimicrobial substances, pain relieving substances, protease inhibitors, and mixtures thereof; and a barrier layer for initially separating the therapeutic agent from a wound fluid in use, wherein the barrier layer comprises a substrate for a lysozyme. Preferably the substrate comprises a chitosan. The barrier layer breaks down in infected or chronic wounds, thereby releasing the therapeutic substance selectively into such wounds.

Fig. 1

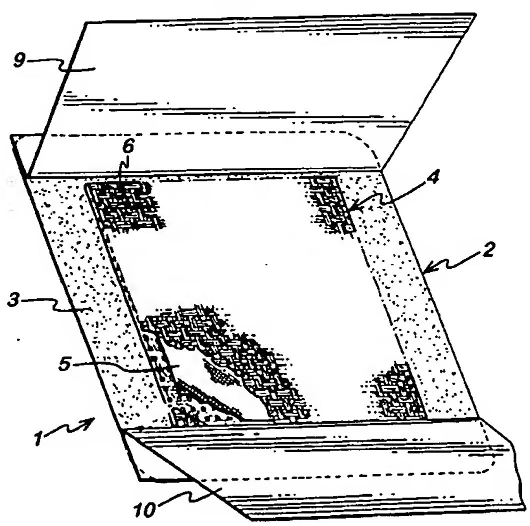

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Fig. 1

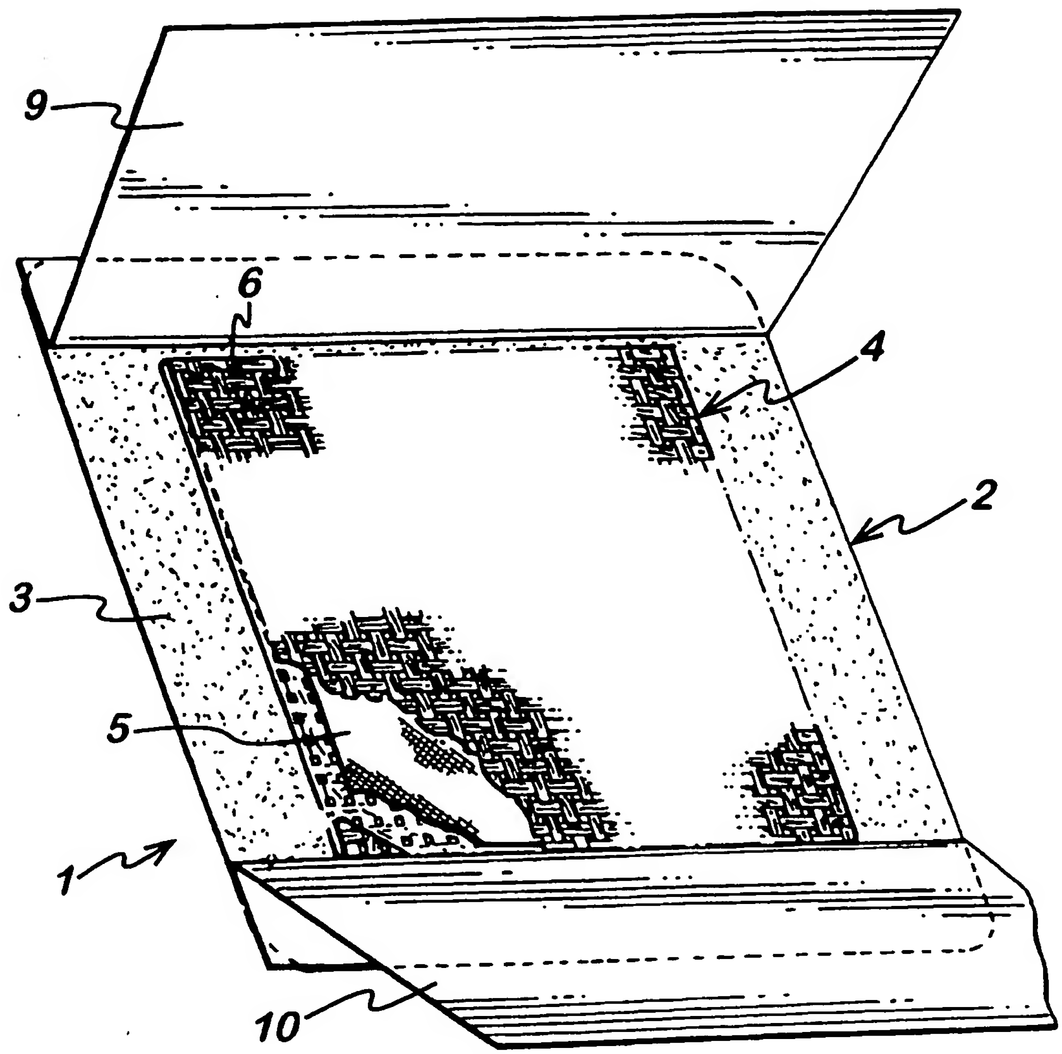
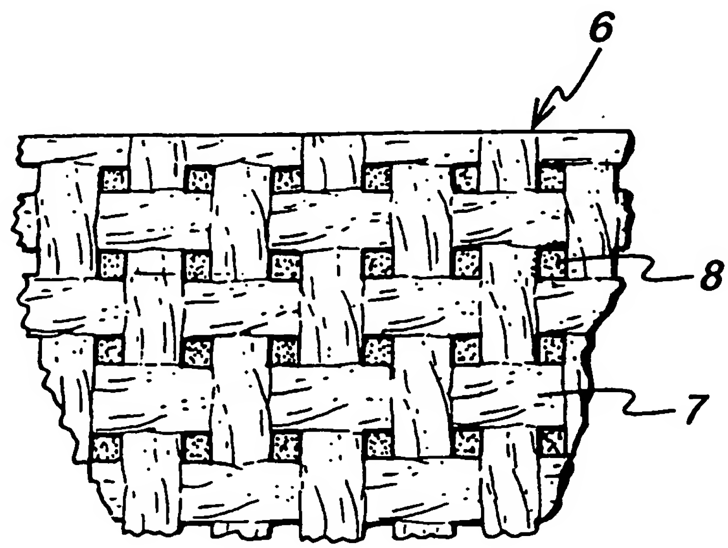


Fig. 2



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WOUND DRESSINGS FOR THE TREATMENT OF WOUND INFECTION

The present invention relates to wound dressing materials, and in particular to new materials for the controlled release of therapeutic agents into wounds.

In mammals, injury triggers an organised complex cascade of cellular and biochemical events that result in a healed wound. Wound healing is a complex dynamic process that results in the restoration of anatomic continuity and function; an ideally healed wound is one that has returned to normal anatomic structure, function and appearance.

Infection of wounds by bacteria delays the healing process, since bacteria compete for nutrients and oxygen with macrophages and fibroblasts, whose activities are essential for the healing of the wound. Infection results when bacteria achieve dominance over the systemic and local factors of host resistance. Infection is therefore a manifestation of a disturbed host/bacteria equilibrium in favour of the invading bacteria. This elicits a systemic septic response, and also inhibits the multiple processes involved in wound healing. Lastly, infection can result in a prolonged inflammatory phase and thus slow healing, or may cause further necrosis of the wound. The granulation phase of the healing process will begin only after the infection has subsided.

Chronically contaminated wounds all contain tissue bacterial flora. These bacteria may be indigenous to the patient or might be exogenous to the wound. Closure, or eventual healing of the wound is often based on a physician's ability to control the level of the bacterial flora.

If clinicians could respond to wound infection as early as possible the infection could be treated topically as opposed to having to use antibiotics. This would also lead to less clinical intervention/hospitalisation and would reduce the use of antibiotics and other complications of infection.

Current methods used to identify bacterial infection rely mainly on judgement of the odour and appearance of a wound. With experience, it is possible to identify an infection in a wound by certain chemical signs such as redness or pain. Some clinicians take swabs that are then cultured in the laboratory to identify specific organisms, but this technique takes time.

Pain is also associated with infected and chronic wounds. Biochemically, pain is experienced when there is an increase of kinins (bradykinin) in the area of the wound. Kinins are produced by the proteolytic breakdown of kininogen, and the protease responsible for this is kallikrein. Kallikrein also stimulates the production of tissue plasminogen activator (t-PA)

It is also known to provide antimicrobial wound dressings. For example, such dressings are known having a liquid permeable wound contacting layer, an intermediate absorbent layer and an outer, liquid-impervious backing layer, in which one or more of the layers contains an antimicrobial agent. For example, EP-A-0599589 describes layered wound dressings having a wound contacting layer of a macromolecular hydrocolloid, an absorbent layer, and a continuous, microporous sheet intermediate the wound contacting layer and the absorbent layer. The absorbent layer contains a low molecular weight antimicrobial agent that can diffuse into the wound.

Copending application GB0027674.1 filed on 13th November 2000 describes wound dressings comprising a liquid-permeable top sheet having a wound facing surface and a back surface, and a hydrogel layer on the wound facing surface of the top sheet. The top sheet is adapted to block or restrict passage of liquid from the back surface to the wound facing surface. The hydrogel layer is an insoluble hydrogel adapted to maintain a moist wound healing environment at the wound surface. The hydrogel may contain therapeutic agents, such as antimicrobial agents, for sustained release into the wound.

Previous antimicrobial wound dressings suffer from the drawback that the release of the antimicrobial agent is relatively unresponsive to the degree of infection of

the wound being treated. This is undesirable because it can result in resistant microorganisms, and also because all unnecessary medication can interfere with the processes of wound healing.

There is thus a need for a wound dressing that will selectively release antimicrobial agents and/or pain relieving agents into infected wounds but not into non-infected wounds, such release into infected wounds taking place preferably even prior to obvious clinical symptoms of infection. Such a dressing would provide early intervention with suitable treatment (e.g. a topical antimicrobial treatment) before wound chronicity sets in.

Copending application GB0126534.7 filed on 5th November 2001 discloses that wound fluid from wounds that are apparently not clinically infected but which go on to become infected within a few days have high levels of neutrophil elastase activity and may also have high levels of other inflammatory enzymes, such as macrophage proteases, other neutrophil proteases, bacterial collagenase, plasmin, hyaluronidase, kallikrein or t-PA. It is also known that chronic wounds, such as venous ulcers, pressure sores and diabetic ulcers have a disordered wound healing metabolism even in the absence of infection. In particular, wound chronicity is associated with elevated levels of protease enzymes in the wound that interfere with the normal processes of tissue formation and destruction in the wound.

The present invention provides a wound dressing comprising: a therapeutic agent selected from the group consisting of antimicrobial substances, pain relieving substances, protease inhibitors, and mixtures thereof; and a barrier layer for initially separating the therapeutic agent from a wound fluid in use, wherein the barrier layer comprises a substrate for a host or bacterially derivec chitinase or chitosanase enzyme.

The antimicrobial agent may, for example, comprise an antiseptic, an antibiotic, or mixtures thereof. Preferred antibiotics include tetracycline, penicillins, terramycins, erythromycin, bacitracin, neomycin, polymycin B, mupirocin, clindamycin and

mixtures thereof. Preferred antiseptics include silver sulfadiazine, chlorhexidine, povidone iodine, triclosan, other silver salts, sucralfate, quaternary ammonium salts and mixtures thereof. The pain relieving agent may be an analgesic or a local anaesthetic.

Preferably, the chitinase or chitosanase enzyme is lysozyme. Lysozyme is a naturally occurring antibacterial enzyme having a molecular weight of about 14.6 kD. It is found in most bodily secretions e.g. tears, mucosa and in the blood in larger amounts. Cellularly it is present in neutrophils and macrophages. In neutrophils it is present in their azurophil (or primary) granules contained in the cytoplasm.

Lysozyme hydrolyses the β 1-4 glycosidic linkage between N-acetyl-glucosamine (NAG) and N-acetylmuramic acid (NAM) in the bacterial cell wall. Alone, lysozyme is primarily active against Gram positive bacteria, which have no outer membrane to protect their cell wall. It has been found that infection is associated with elevated levels of lysozyme. Typical measured lysozyme levels are 8μg/ml for uninfected serum and 192μg/ml for infected wound fluid. This invention uses the elevated levels of lysozyme in infected wound fluid relative to non-infected wound fluid as a trigger to release a suitable therapeutic agent from the dressing into the wound.

The barrier layer is separate from the therapeutic agent, and the therapeutic agent is initially prevented from contacting the wound fluid by the barrier layer. That is to say, the bioavailability of the therapeutic agent to the wound surface is low until the barrier material has been broken down by lysozyme in the wound fluid, at which point the bioavailability increases sharply. Since the lysozyme levels are elevated in infected wounds, this provides for accelerated and/or selective release of the therapeutic agent into such wounds. The barrier layer is normally substantially impervious to wound fluid and insoluble therein unless the wound fluid contains a sufficient level of the lysozyme to break down the substrate material.

The barrier material may be any material that is broken down by a chitinase or chitosanase enzyme such as lysozyme. Typically, the barrier material comprises a polysaccharide substrate for lysozyme, and preferably the polysaccharide comprises D-glucosamine or N-acetyl D-glucosamine residues. Preferably, the polysaccharide comprises chitin or chitosan.

Chitin is a natural biopolymer composed of N-acetyl-D-glucosamine units. Chitin may be extracted from the outer shell of shrimps and crabs in known fashion. The chitin is then partially deacetylated, for example by treatment with 5M-15M NaOH, to produce chitosan. Complete deacetylation of the chitin is not a practical possibility, but preferably the chitosan is at least 50% deacetylated, more preferably at least 75% deacetylated. Chitosan has been employed for wound treatment in various physical forms, e.g. as a solution/gel; film/membrane; sponge; powder or fiber. Chitosan in the free base form is swellable but not substantially soluble in water at near-neutral pH, but soluble in acids due to the presence of ammonium groups on the chitosan chain. The solubility of the chitosan may be reduced by cross-linking, for example with epichlorhydrin. The solubility may also be modified by complexation with polyanions, such as sodium alginate. Typically, the average molecular weight of the chitosan as determined by gel permeation chromatography is from about 10^5 to about 10^6.

The barrier layer is preferably about 0.1 to about 3 mm thick. Preferably about 0.5 to 1.5 mm thick. The enzyme substrate material may be combined in a film-forming composition with additional polymeric materials, plasticisers, and humectants. Suitable polymers include alginates, guar gum, carboxymethyl cellulose, methyl cellulose, hydroxypropyl methyl cellulose, locust bean gum, carrageenan, heparan sulfate, dermatan sulfate, glycosaminoglycans such as hyaluronic acid, proteoglycans, and mixtures thereof. Suitable plasticisers include C2-C8 polyhydric alcohols such as glycerol. Preferably the enzyme substrate compounds make up at least about 10% by weight, more preferably at least about 20%, 30%, 40%, 50%, 60% or 75% by weight of the film-forming barrier composition. Since the levels of proteases are elevated in non-infected chronic wounds, the barrier layers of the dressings according to the present invention

preferably are not broken down by protease enzymes present in wound fluid such as elastase, macrophage proteases, other neutrophil proteases, bacterial collagenase, plasmin, hyaluronidase, kallikrein or t-PA. Preferably, the barrier layer materials in the dressings according to the present invention comprise less than 25% by weight, preferably less than 10% by weight, of substrates for such protease enzymes such as gelatin, collagen or elastin.

In certain embodiments the barrier layer comprises a substantially continuous film comprising the film forming composition of the enzyme substrate as described above.

In other embodiments the barrier layer comprises an apertured sheet having a composition comprising the substrate material applied thereto in occlusive fashion. The occlusive composition may be similar to the film-forming composition described above. In these embodiments, the apertures typically make up from about 0.1% to about 50% of the area of the wound facing surface of the sheet before swelling, more typically from about 1% to about 30% of the area of the apertured sheet, and preferably from about 10% to about 25% of the area of the apertured sheet. Typically, the apertured sheet has from about 1 to about 30 apertures per square cm, for example from about 4 to about 15 apertures per square cm or from about 5 to about 10 apertures per square cm. In certain embodiments the apertures are uniformly distributed over the surface of the sheet, preferably in a regular pattern. The mean area of each aperture may for example be from about 0.01 to about 10 mm^2, preferably from about 0.1 to about 4 mm^2, and more preferably from about $1mm^2$ to about $2mm^2$. It will be appreciated that the sheet may include more than one size and shape of aperture in order to provide apertures that open more or less quickly on exposure to infected wound fluid. This enables still more control over the dynamics of therapeutic agent delivery to the wound. Typically, substantially the whole area of the apertures in the the apertured sheet is blocked by the barrier material before exposure to wound exudate

Preferably, the thickness of the barrier film or the apertured sheet (by ASTM D374-79) is from about 0.2 to about 5 mm, more preferably from about 0.4 to about 3 mm.

For example, the barrier layer material may further comprise a polymer selected from the group consisting of water soluble macromolecular materials (hydrogels) such as sodium alginate, sodium hyaluronate, alginate derivatives such as the propylene glycol alginate described in EP-A-0613692, and soluble hydropolymers formed from vinyl alcohols, vinyl esters, vinyl ethers and carboxy vinyl monomers, meth(acrylic) acid, acrylamide, N-vinyl pyrrolidone, acylamidopropane sulphonic acid, PLURONIC (Registered Trade Mark) (block polyethylene glycol, block polypropylene glycol) polystyrene-, maleic acid, NN-dimethylacrylamide diacetone acrylamide, acryloyl morpholine, and mixtures thereof. Suitable hydrogels are also described in US-A-5352508.

The barrier layer material may further comprise a polymer selected from the group consisting of bioerodible polymers such as polylactide/polyglycolide, collagen, gelatin, polyacrylate gels such as those described in EP-A-0676457, calcium alginate gels, cross-linked hyaluronate gels, gels of alginate derivatives such as propylene glycol alginate, and gels wherein the hydropolymer is formed from vinyl alcohols, vinyl esters, vinyl ethers and carboxy vinyl monomers, meth(acrylic) acid, acrylamide, N-vinyl pyrrolidone, acylamidopropane sulphonic acid, PLURONIC (Registered Trade Mark) (block polyethylene glycol, block polypropylene glycol) polystyrene-, maleic acid, NN-dimethylacrylamide diacetone acrylamide, acryloyl morpholine, and mixtures thereof. Suitable hydrogels are also described in US-A-5352508.

The barrier layer material may further comprise from about 5 to about 75% by weight, preferably from 15 to 40% by weight, on the same basis of one or more humectants such as glycerol. The barrier layer material may further contain up to about 30% w/w, more preferably up to about 15% w/w on the same basis of water.

In certain embodiments wound dressings have a layered structure wherein preferably a layer of the antimicrobial substance is provided behind the barrier layer. That is to say, on the side of the barrier layer opposite to the wound facing surface of the barrier layer in use. The layer of antimicrobial substance may contact the barrier layer directly, or may be separated therefrom for example by an absorbent layer.

Preferably, the barrier sheet according to these embodiments of the invention forms part of a layered wound dressing having the antimicrobial material disposed on the side of the barrier sheet opposite to the wound facing side of the barrier sheet.

Preferably, the layered wound dressing further comprises an absorbent layer and/or a backing layer.

The area of the optional absorbent layer is typically in the range of from $1cm^2$ to $200cm^2$, more preferably from $4cm^2$ to $100cm^2$.

The optional absorbent layer may be any of the layers conventionally used for absorbing wound fluids, serum or blood in the wound healing art, including gauzes, nonwoven fabrics, superabsorbents, hydrogels and mixtures thereof. Preferably, the absorbent layer comprises a layer of absorbent foam, such as an open celled hydrophilic polyurethane foam prepared in accordance with EP-A-0541391, the entire content of which is expressly incorporated herein by reference. In other embodiments, the absorbent layer may be a nonwoven fibrous web, for example a carded web of viscose staple fibers. The basis weight of the absorbent layer may be in the range of $50\text{-}500g/m^2$, such as $100\text{-}400g/m^2$. The uncompressed thickness of the absorbent layer may be in the range of from 0.5mm to 10mm, such as 1mm to 4mm. The free (uncompressed) liquid absorbency measured for physiological saline may be in the range of 5 to 30 g/g at 25°. In certain embodiments the antimicrobial material may be dispersed in or on the absorbent layer.

Preferably, the dressing further comprises a backing layer covering the barrier sheet and the optional absorbent layer on the side opposite the wound-facing side of the dressing. The backing layer preferably provides a barrier to passage of microorganisms through the dressing and further preferably blocks the escape of wound fluid from the dressing. The backing layer may extend beyond at least one edge of the barrier sheet and optional absorbent layer to provide an adhesive-coated margin adjacent to the said edge for adhering the dressing to a surface, such as to the skin of a patient adjacent to the wound being treated. An adhesive-coated margin may extend around all sides of the barrier sheet and optional absorbent layer, so that the dressing is a so-called island dressing. However, it is not necessary for there to be any adhesive-coated margin.

Preferably, the backing layer is substantially liquid-impermeable. The backing sheet is preferably semipermeable. That is to say, the backing sheet is preferably permeable to water vapour, but not permeable to liquid water or wound exudate. Preferably, the backing sheet is also microorganism-impermeable. Suitable continuous conformable backing sheets will preferably have a moisture vapor transmission rate (MVTR) of the backing sheet alone of 300 to 5000 $g/m^2/24hrs$, preferably 500 to 2000 $g/m^2/24hrs$ at 37.5 C at 100% to 10% relative humidity difference. The backing sheet thickness is preferably in the range of 10 to 1000 micrometers, more preferably 100 to 500 micrometers.

Suitable polymers for forming the backing sheet include polyurethanes and poly alkoxyalkyl acrylates and methacrylates such as those disclosed in GB-A-1280631. Preferably, the backing sheet comprises a continuous layer of a high density blocked polyurethane foam that is predominantly closed-cell. A suitable backing sheet material is the polyurethane film available under the Registered Trade Mark ESTANE 5714F.

The adhesive layer (where present) should be moisture vapor transmitting and/or patterned to allow passage of water vapor therethrough. The adhesive layer is preferably a continuous moisture vapor transmitting, pressure-sensitive adhesive layer of the type conventionally used for island-type wound dressings, for example,

a pressure sensitive adhesive based on acrylate ester copolymers, polyvinyl ethyl ether and polyurethane as described for example in GB-A-1280631. The basis weight of the adhesive layer is preferably 20 to 250 g/m^2, and more preferably 50 to 150 g/m^2. Polyurethane-based pressure sensitive adhesives are preferred.

Preferably, the adhesive layer extends outwardly from the absorbent layer and the envelope to form an adhesive-coated margin on the backing sheet around the absorbent layer as in a conventional island dressing.

Also within the scope of the present invention are embodiments in which the barrier layer substantially encapsulates the antimicrobial substance. For example, the active substance may be dissolved or dispersed in the material making up the barrier layer sheet. In other embodiments, the dressing may comprise, or consist essentially of, particles such as microspheres of antimicrobial material encapsulated in a layer comprising the substrate material. The particles are preferably loaded with from 1 to 90 wt.%, more preferably from 3 to 50 wt.% of the antimicrobial agents.

The particles may be made by any suitable technique, including comminution, coacervation, or two-phase systems for example as described in US-A-3886084. Techniques for the preparation of medicated microspheres for drug delivery are reviewed, for example, in Polymeric Nanoparticles and Microspheres, Guiot and Couvreur eds., CRC Press (1986).

A preferred method for preparation of the microparticles is coacervation, which is especially suited to the formation of particles in the preferred size range of 100 to 500 micrometers having a high loading of therapeutic agents. Coacervation is the term applied to the ability of a number of aqueous solutions of colloids, to separate into two liquid layers, one rich in colloid solute and the other poor in colloid solute. Factors which influence this liquid-liquid phase separation are: (a) the colloid concentration, (b) the solvent of the system, (c) the temperature, (d) the addition of another polyelectrolyte, and (e) the addition of a simple electrolyte to the solution. Coacervation can be of two general types. The first is called "simple" or "salt"

coacervation where liquid phase separation occurs by the addition of a simple electrolyte to a colloidal solution. The second is termed "complex" coacervation where phase separation occurs by the addition of a second colloidal species to a first colloidal solution, the particles of the two dispersed colloids being oppositely charged. Generally, materials capable of exhibiting an electric charge in solution (i.e. materials which possess an ionizable group) are coacervable. Such materials include natural and synthetic macromolecular species such as gelatin, acacia, tragacanth, styrene-maleic anhydride copolymers, methyl vinyl ether-maleic anhydride copolymers, polymethacrylic acid, and the like.

If, prior to the initiation of coacervation, a water-immiscible material, such as an oil, is dispersed as minute droplets in an aqueous solution or sol or an encapsulating colloidal material, and then, a simple electrolyte, such as sodium sulfate, or another, oppositely charged colloidal species is added to induce coacervation, the encapsulating colloidal material forms around each oil droplet, thus investing each of said droplets in a liquid coating of the coacervated colloid. The liquid coatings which surround the oil droplets must thereafter be hardened by cross-linking to produce solid-walled microcapsules

Preferably, the wound dressing according to any aspect of the present invention is sterile and packaged in a microorganism-impermeable container.

An embodiment of the present invention will now be described further, by way of example, with reference to the accompanying drawings, in which:
Figure 1 shows a perspective view of the lower (wound contacting) surface of a wound dressing according to the invention with the wound contacting sheet according to the invention partially cut away; and
Figure 2 shows a plan view of a portion of the wound contacting sheet according to the invention from the dressing of Fig. 1.

Referring to Figure 1, the wound dressing 1 is an island-type self-adhesive wound dressing comprising a backing layer 2 of microporous liquid-impermeable polyurethane foam, such as ESTANE 5714F (Registered Trade Mark). The

backing layer is permeable to water vapor, but impermeable to wound exudate and microorganisms.

The backing layer 2 is coated with a substantially continuous layer 3 of pressure-sensitive polyurethane adhesive. An absorbent island 4 containing the antimicrobial is adhered to a central region of the adhesive-coated backing sheet 2.

The absorbent island 4 comprises an absorbent layer 5 of gauze having a basis weight of about $250g/m^2$ and impregnated with silver sulfadiazine in an amount of about $25g/m^2$.

A wound contacting barrier sheet 6 extends over the absorbent layer 5 and is wrapped around the absorbent layer 5, and adhered to the backing layer 2 behind the absorbent layer 5 by the adhesive 3. The wound contacting sheet 6 consists of a support layer 7 of a perforated polypropylene film with 12 perforations per cm^2 in which the apertures 8 are occluded by a lysozyme-degradable film composition prepared as follows.

100.0 grams of chitosan chloride was mixed in 1.5 liters of water until blended. 200.0 grams of glycerol were blended into the mixture, after which 200.0 grams of polyethylene glycol ("PEG") were then added. The resulting mixture was then filtered and coated onto the bottom of a PTFE tray to a thickness of about 1mm.

At this stage the perforated polypropylene film with 12 perforations per cm^2 was placed on the surface of the chitosan dispersion. The sheet having the dispersion in the apertures thereof was then partially dried and peeled from the tray. The resulting sheet material had the apertures of the polypropylene film occluded by a thin film of the chitosan composition. The sheet material was then immersed in a coagulation bath of aqueous NaOH at pH13 to swell and coagulate (neutralise) the chitosan, followed by washing in deionized water (pH7) and drying.

The wound facing surface of the dressing shown in Figure 1 is protected by two silicone-coated release papers 9,10. The dressing is packaged in a microorganism-impermeable pouch (not shown), and sterilised using gamma radiation.

In use, the dressing 1 is removed from the package, the release papers 9,10 are removed, and the dressing is adhered to the skin around the wound by the adhesive layer 3, with the wound contacting sheet in contact with the wound to provide a sterile and absorbent dressing. The dissolution of the chitosan in the presence of elevated levels of lysozyme triggers the release of antimicrobial active agent from the absorbent layer into the wound in response to increased lysozyme production by infected or chronic wounds. This has the further benefit of allowing excess exudate to escape through the perforated sheet 7 into the absorbent layer 5.

The above embodiment has been described by way of example only. Many other embodiments falling within the scope of the accompanying claims will be apparent to the skilled reader.

CLAIMS

1. A wound dressing comprising: a therapeutic agent selected from the group consisting of antimicrobial substances, pain relieving substances, protease inhibitors, and mixtures thereof; and a barrier layer for initially separating the therapeutic agent from a wound fluid in use, wherein the barrier layer comprises a substrate for a host or bacterially derived chitinase or chitosanase.

2. A wound dressing according to claim 1, wherein the substrate is a substrate for a lysozyme.

3. A wound dressing according to claim 1 or 2, wherein the therapeutic substance comprises an antiseptic, an antibiotic, an analgesic, a local anaesthetic, a protease inhibitor, or mixtures thereof.

4. A wound dressing according to claim 3, wherein the therapeutic substance comprises an antiseptic selected from the group consisting of chlorhexidine, silver sulfadiazine, povidone iodine, silver salts, triclosan, sucralfate, quaternary ammonium salts, and mixtures thereof.

5. A wound dressing according to claim 3, wherein the therapeutic substance comprises an antibiotic selected from the group consisting of tetracycline, penicillins, terramycins, erythromycin, bacitracin, neomycin, polymycin B, mupirocin, clindamycin and mixtures thereof.

6. A layered wound dressing material according to any preceding claim, further comprising a liquid-impermeable backing layer over the therapeutic substance and the barrier layer.

7. A wound dressing according to claim 6, wherein the backing layer is adhesive-coated and provides an adhesive-coated margin around the therapeutic substance and the barrier layer.

8. A wound dressing according to any preceding claim, further comprising an absorbent layer.

9. A wound dressing according to any preceding claim, wherein the barrier layer comprises a substantially continuous film comprising the substrate material.

10. A wound dressing according to any preceding claim, wherein the barrier layer comprises an apertured sheet having a composition comprising the substrate material applied thereto in occlusive fashion.

11. A wound dressing according to claim 9 or 10, wherein a layer of the therapeutic substance is provided behind the barrier layer.

12. A wound dressing according to claim 10, wherein an absorbent layer is provided behind the barrier layer and the therapeutic substance is dispersed in the absorbent layer.

13. A wound dressing according to any one of claims 1 to 7, wherein the barrier layer substantially encapsulates the therapeutic substance.

14. A wound dressing according to any preceding claim, wherein the substrate material comprises chitin or chitosan.

The Patent Office

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Application No: GB 0221064.9
Claims searched: 1-14

Examiner: Dr William Thomson
Date of search: 13 February 2003

Patents Act 1977 : Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance	
X	1-14	EP 0599589A1	(JOHNSON & JOHNSON MEDICAL INC.) See whole document, in particular column 5, lines 8-13, column 6, lines 18-25 and claims 7 and 14
X	1-14	EP 0371736A2	(MITSUBISHI KASEI CORPORATION) See whole document, in particular page 2, lines 37-42, page 5, lines 3-29 and claims 1-11
X	1-14	EP 0475807A2	(TERUMO KABUSHIKI KAISHA) See whole document, in particular page 3, line 34-58, page 4, lines 19-21 and claims 1-13
A		WO 02/072163A1	(KIMBERLY-CLARK WORLDWIDE) See whole document, in particular claims 1, 11, 14 and 17

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{V}:

A5B

Worldwide search of patent documents classified in the following areas of the IPC^{7}:

A61K

The following online and other databases have been used in the preparation of this search report:

CAS-ONLINE, EPODOC, JAPIO & WPI